

# Lethal metatropic dwarfism: a case report

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## ABSTRACT

With the improved resolution of ultrasound machines, fetal limb studies can be conducted early in pregnancy. The finding of a “short femur” (<3rd centile) on ultrasound prompts obstetricians to initiate antenatal investigations to allow better counseling about the prognosis of the newborn. The following workup is indicated: advanced ultrasound to identify various characteristics of the fetus, amniocentesis for karyotyping and genetic analysis for bone diseases, and serial imaging of the skeleton at birth.

## KEYWORDS

Dwarfism, metatropic, short femur, prenatal diagnosis.

## Introduction

The organogenesis of the limb skeleton starts at between 7 and 10 weeks of gestation. However, screening for severe limb anomalies is feasible between 12 and 26 weeks of gestation. Morphological study of the limbs remains a difficult examination, which must also take fetal mobility into account. We report the case of a fetus presenting a very rare form of dwarfism, metatropic dwarfism, and suggest a plan of action to manage the finding of a short femur (<3<sup>rd</sup> percentile) on prenatal ultrasound.

## Case report

This report describes the case of a 22 1/7 weeks gestational age male fetus presenting with several abnormalities suggestive of bone pathology during a routine second trimester scan: very

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short long bones corresponding to measurements for 18 weeks of gestation (Figures 1 and 2), associated with fetal hydrops and subcutaneous edema, especially on the forehead (Figures 3 and 4), mild ascites and pleural effusion.

The placenta, amniotic fluid, fetal mobility and Doppler recordings were reported as normal. The non-invasive prenatal test performed at the end of the first trimester was reported as normal (very low risk for trisomy 13, 18 and 21). An amniocentesis at 22 3/7 weeks of gestation did not show any chromosomal abnormality within the limits of resolution of a CGH array (arr(1-22)x2,(X,Y)x1). Fibroblast growth factor receptor

**Figure 1** Short femur.



**Figure 2** Short humerus.



**Figure 3** Fetal profile with pre-frontal edema.**Figure 4** Pre-frontal edema in 3D reconstruction.

3 analysis was normal, excluding thanatophoric dysplasia. Fetal death in utero was observed at 25 2/7 weeks of gestation and delivery was induced according to a classic regimen of mifepristone followed by misoprostol.

The fetal autopsy findings pointed to a diagnosis of metatropic dwarfism. Several characteristic features were found (Figure 5): brachycephalic face, complete cleft palate, trunk of normal height, but narrow and barrel shaped, short limbs with peri-articular nodules causing significant ankylosis, long and slender fingers and toes with hypoplasia of the terminal phalanges.

No abnormalities of the internal organs of the fetus were seen. The placenta was reported as mildly hypertrophic. Post-mortem X-ray imaging (Figure 6) also suggested metatropic dysplasia, showing narrow thorax, defective ossification of the vertebral bodies and deformed capital femoral epiphyses with hyperplasia of proximal femoral metaphyses.

**Figure 5** Post-mortem photo.

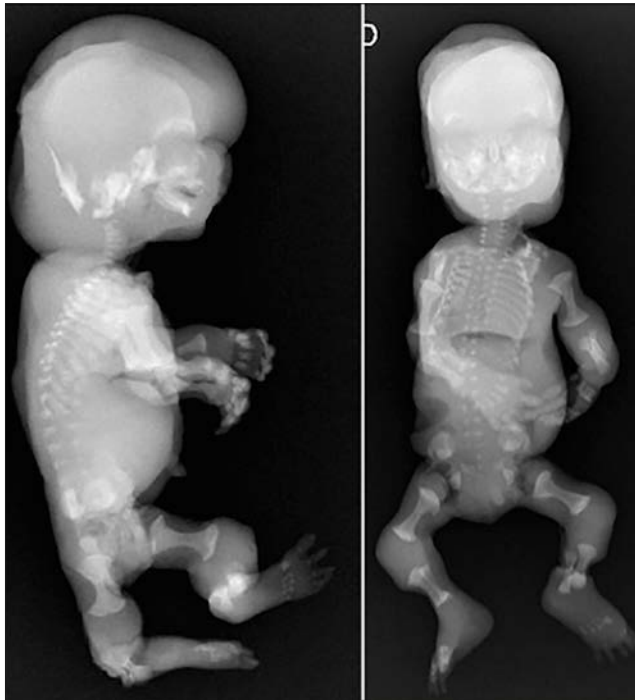
This diagnosis was confirmed by genetic analysis which revealed a *de novo* c.2219G>T mutation of the transient receptor potential vanilloid 4 gene (TRPV4). Post-test counseling confirmed a low recurrence risk, estimated at 1-2%, as parental mosaicism was not excluded.

## Discussion

Metatropic dwarfism, or dysplasia, is a spondylo-epi-metaphyseal dysplasia, characterized by short limbs with normal-height trunk, enlargement of the joints, and kyphoscoliosis. It is a very rare form of dwarfism with a prevalence estimated at less than 1/1,000,000<sup>[1]</sup>.

The etiology is due to mutations in TRPV4. Transmission can be recessive or dominant<sup>[2]</sup>. These mutations induce an increase in calcium in the chondrocytes, which disrupts endochondral ossification. The term metatropic derives from the Greek “metatropos”, which means “variable” and underlines the clinical and radiological changes that occur over time. During growth, the non-lethal variant of metatropic dwarfism is associated with progressive kyphoscoliosis relative to elongation of the limbs.

This pathology was first described by Maroteaux<sup>[3]</sup> in 1966. The term metatropic dysplasia covers fibrochondrogenesis, Schneckenbecken dysplasia, and several forms of metatropic dysplasia, which were classified into 4 types according to their severity by Kozlowski *et al.*<sup>[4]</sup>:

**Figure 6** Profile and front view radiographs.

**Type 1:** is perinatally lethal and also described as «lethal hyperplastic metatropic dysplasia»;

**Type 2:** is generally perinatally lethal or lethal in early childhood. This type is known as «lethal metatropic dysplasia» or «hyperchondrogenesis», and it is transmitted autosomal recessively;

**Type 3:** a severe «metatropic dysplasia» where survival is described and transmission is autosomal dominant;

**Type 4:** various types of different spondylo-epi-metaphyseal dysplasias appearing with mild metatropic changes.

The striking ultrasound sign in the rare case of metatropic dysplasia here presented was the short femur. We here propose a brief checklist for the gynecologist, for application if a “short femur” is observed prenatally.

The initial assessment of a “short femur”, or long bone below the 3<sup>rd</sup> percentile seen on antenatal ultrasound, should include the following steps:

- Review the dating of the pregnancy, with evaluation of the measurements of an early first trimester ultrasound.
- Family anamnesis. Short parental stature is reassuring when short femur on ultrasound is observed as an isolated finding. This leads to a diagnosis of “constitutional short femur”.
- Doppler exams to rule out growth retardation caused by placental insufficiency.
- Antenatal diagnostic imaging with ultrasound to screen for other malformations and look for features of syndromic dwarfism. Curvature of the long bones and the shape of the skull are essential elements to consider. It is therefore advisable to measure:
  1. Length of the femur (FL), the humerus (HL) and foot (an FL/foot ratio <1 suggests osteochondrodysplasia). Subjective estimation of bone mineralization on ultrasound is acceptable but a bone CT scan is more useful.
  2. Limb segment measurements (hand, forearm and arm) differentiate the mesomelic (shortened forearm), rhizomelic

(shortened arm) or micromelic (all 3 segments are shortened) forms as well as the polydactyly-short ribs syndromes.

3. The thoraco-abdominal index is a measurement used in fetal prognosis. A value less than 0.6 indicates a poorer prognosis. Bilateral visualization of the femur and humerus is recommended to exclude asymmetrical forms of skeletal malformation (i.e., toxic, vascular, amniotic bands or syndromic).
4. Amniocentesis for chromosomal and genetic analyses.

## Conclusions

Skeletal malformations including metatropic forms are rare pathologies in prenatal screening. A short femur on second trimester screening puts the obstetrician and the family physician in a difficult situation, given the need to counsel the parents about the disease and the outcome of their child.

Therefore, it is advisable to exclude lethal skeletal pathologies and to adopt a multidisciplinary approach to skeletal anomalies with medium- and long-term prognosis, including genetic counseling for the couple.

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**Conflict of Interest:** The authors declare that there is no conflict of interest.